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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/912,252	07/25/2001	Ed Croze	BERLX-79	4123
23599	7590	02/11/2004	EXAMINER - /	
MILLEN, WHITE, ZELANO & BRANIGAN, P.C. 2200 CLARENDON BLVD. SUITE 1400 ARLINGTON, VA 22201			NGUYEN, QUANG	
			ART UNIT	PAPER NUMBER
			1636	

DATE MAILED: 02/11/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/912,252

Applicant(s)

CROZE ET AL.

Examiner

Quang Nguyen, Ph.D.

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 17 July 2003 and 20 November 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-21 is/are pending in the application.
- 4a) Of the above claim(s) 5 and 15-21 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-4 and 6-14 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
* See the attached detailed Office action for a list of the certified copies not received.
- 13) ☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.
a) ☐ The translation of the foreign language provisional application has been received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s) _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____

DETAILED ACTION

Claims 1-21 are pending in the present application.

Applicant's election with traverse of Group I (claims 1-4 and 6-14), drawn to a method of potentiating the effects of a type I IFN on a target cell population comprising increasing the number of functional IFNAR2c receptor chains on the surface of modified cells within the target cell population and then exposing the modified cells to a therapeutically effective amount of a type I IFN, wherein the up-regulation of gene expression of the IFNAR2c gene is accomplished by introducing an exogenous gene encoding the IFNAR2c polypeptide, in a Response to Restriction Requirement dated 7/17/03 is acknowledged. The traversal is on the ground(s) that the Examiner has not demonstrated that an undue searching burden would be required to examine the full scope of the claims. This is not found persuasive because the methods of Groups I-V are distinct one from the others as they are drawn to methods having different starting materials, method steps and different technical considerations for achieving the desired end-results. Additionally, these different inventions have acquired a separate status in the art as a separate subject for inventive effect and that they require independent searches.

The requirement is still deemed proper and is therefore made FINAL.

Upon further consideration, the species restriction is withdrawn.

Claims 5 and 15-21 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic

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or linking claim. Applicant timely traversed the restriction (election) requirement in the Response dated 7/17/03.

Claims 1-4 and 6-14 are examined on the merits herein.

Claim Objections

Claim 1 is objected to because the terms "IFN" and "IFNAR2c" should be spelled out at the first occurrence of the terms. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 and 6-14 are rejected under 35 U.S.C. 112, first paragraph, because with respect to the elected invention the specification, while being enabling for:

A method of potentiating anti-growth or anti-viral effects of a type I interferon (IFN) on cells in a target cell population, said method comprises introducing directly into said cells an exogenous gene encoding an interferon receptor 2c receptor polypeptide (IFNAR2c) and then exposing the modified cells to a therapeutically effective amount of a type I IFN, and wherein the number of functional IFNAR2c receptor polypeptides on the surface of the modified cells is increased;

does not reasonably provide enablement for a method of potentiating any effects of a type I IFN on a cells of a target cell population by introducing onto said cells an

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exogenous gene encoding the IFNAR2c polypeptide by any route of delivery. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in the determination of an enabling disclosure have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art and the breadth of the claims. *Ex parte Forman*, (230 USPQ 546 (Bd Pat. Appl & Unt, 1986); *In re Wands*, 858 F.2d 731, 8 USPQ 2d 1400 (Fed. Cir. 1988)).

With respect to the elected invention, the claims are drawn to a method of potentiating the effects of a type I IFN on a target cell population comprising introducing an exogenous gene encoding the IFNAR2c polypeptide into cells within the target cell population for increasing the number of functional IFNAR2c receptor chains on the surface of the modified cells and then exposing the modified cells to a therapeutically effective amount of a type I IFN.

The specification teaches by exemplification showing that various tumor cell lines (HT1080 cells, U5A cells, MDA231 cells) exhibit enhanced sensitivity to the antiproliferative effects (including apoptosis) of IFN β 1b or IFN α upon transfection with an IFNAR2c gene. Applicants further demonstrated that LOX human melanoma cells transfected with an IFNAR2c gene are also more sensitive to the *in vivo* anti-growth activity of IFN β 1b than the parental cells. The above evidence has been noted and

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considered. However, the evidence is not reasonably extrapolated to the instant broadly claimed invention for the following reasons.

(1) The breadth of the claims. With respect to the elected invention, the instant claims encompass a method of potentiating any effects of a type I IFN on any target cell population comprising increasing the number of functional IFNAR2c receptor chains on the surface of modified cells within the target cell population by introducing an exogenous gene encoding the IFNAR2c polypeptide into the modified cells by any route of delivery, and then exposing the modified cells to a therapeutically effective amount of a type I IFN.

(2) The state and unpredictability of the prior art. The nature of the elected invention falls within the realm of gene therapy. At the effective filing date of the present application, the attainment of any desired therapeutic effect (for this instance potentiating the effects of a type I IFN on a target cell population) remains unpredictable. Particularly, vector targeting *in vivo* to targeted cells, tissues or organ continues to be inefficient and unpredictable. This is supported by numerous teachings available in the art. Dang et al. (Clin. Cancer Res. 5:471-474, 1999) noted that further advancement in all fields such as gene delivery, gene expression and host immune manipulation is needed to make gene therapy a reality. Dang et al. pointed out several factors limiting an effective gene therapy, including sub-optimal vectors, the lack of a stable *in vivo* transgene expression, the adverse host immunological responses to the delivered vectors and most importantly an efficient gene delivery to target tissues or cells (last paragraph, col. 2, page 474). Verma & Somia (Nature 389:239-242, 1997)

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reviewed various vectors known in the art for use in gene therapy and the problems which are associated with each and clearly indicated that resolution to *in vivo* vector targeting had not been achieved in the art (see the entire article). Verma & Somia also discussed the role of the immune system in inhibiting an efficient targeting of viral vectors to desired target cells (see page 239, and second and third columns of page 242). More recent reviews by Romano et al. (Stem Cells 18:19-39, 2000) and Xu et al. (Clin. Cancer Res. 7:3314-3324, 2001) also support the lack of an efficient gene delivery to target tissues or cells by any route of delivery to obtain the desired therapeutic effects.

Additionally, at the effective filing date of the present application little was known on the use of an exogenous gene encoding the IFNAR2c polypeptide for potentiating any effects of a type I IFN on any target cell population as evidenced by the teachings of Johns et al. (U.S. Patent No. 5,681,558), Novick et al. (U.S. Patent No. 5,821,078), Domanski et al. (J. Biol. Chem. 273:3144-3147, 1998) and Chen et al. (U.S. Patent No. 6,569,420).

(3) The amount of direction or guidance provided. Apart from the exemplification showing that the increased exogenous expression of functional IFNAR2c receptor polypeptides in various transfected cancer cell lines resulted in enhanced sensitivity of the transfected cells to the antiproliferative effects (including enhanced apoptosis) of IFN β 1b or IFN α , the instant specification fails to provide sufficient guidance for a skilled artisan on how to attain any other potentiating effects of a type I interferon. Despite similarities of all type I interferons to bind to the same type I interferon receptor, it

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should be noted that the biological responses stimulated by type I interferons are significantly different. Therefore, it is not clear that the increase in exogenous expression of IFNAR2c receptor in a target cell population would necessarily potentiate every effect of a type I IFN. Since the prior art at the effective filing date of the present disclosure does not provide such guidance, it is incumbent upon the instant specification to do so. Additionally, the present application fails to provide sufficient guidance for a skilled artisan on how to overcome obstacles associated with *in vivo* vector targeting known in the art as discussed above, so that cells of a target cell population can be transfected efficiently with an exogenous gene encoding the IFNAR2c polypeptide by any route of administration to yield the desired therapeutic effects. In light of the state of the art and given the lack of sufficient guidance provided by the present application, it would have required undue experimentation for a skilled artisan to make and use the method as claimed.

(4) Working example provided. The specification fails to provide any example showing any potentiating effects of a type I IFN other than the enhanced anti-growth effects by the exogenous expression of the gene encoding the IFNAR2c polypeptides nor does it provide any example demonstrating that *in vivo* vector targeting has been attained.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the breadth of the claims, and the unpredictability of the gene therapy art, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 11 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 11, it is unclear what is encompassed by the term "derived from". It is unclear the nature and number of steps required to obtain a "derivative" of a retrovirus or an adenovirus. The term implies a number of different steps that may or may not result in a change in the functional characteristics of a viral vector from the source that it is "derived from". It would be remedial to amend the claim language to recite - - the viral vector is a retroviral or adenoviral vector - -.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-4, 6 and 12-13 are rejected under 35 U.S.C. 102(b) as being anticipated by Domanski et al. (J. Biol. Chem. 273:3144-3147, 1998).

Domanski et al. teach a method for inducing an antiviral state in mouse L-929 cells stably coexpressing the wild type α subunit with a β L chain (or IFNAR2c receptor

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chain) truncated at amino acid 462, 417, or 346 (in the form of a recombinant plasmid) by exposing the transfected cells to muIFN $\alpha\beta$, huIFN β and huIFN α at various IFN concentrations (8 units to >500 units/mL; see page 3145, particularly Table 1). Since the IFN concentrations utilized by Domanski et al. fall within a therapeutically effective amount of a type I IFN of the present invention (see 50, 500 or 5000 IU/mL, see example 3), it is inherent that the method taught by Domanski et al. also results in enhanced anti-growth effect. Therefore, the method taught by Domanski et al. meets every limitation of the instant claims as written.

Accordingly, Domanski et al. anticipate the instant claims.

Conclusions

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Quang Nguyen, Ph.D., whose telephone number is (571) 272-0776.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, David Guzo, Ph.D., may be reached at (571) 272-0767, or SPE, Irem Yucel, Ph.D., at (571) 272-0781.

To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1636.

Quang Nguyen, Ph.D.


JAMES KETTER
PRIMARY EXAMINER